UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/516,779	06/29/2005	Kevin L. Rozwadowski	4810-69922-01	5541

24197 7590 03/22/2007

KLARQUIST SPARKMAN, LLP
121 SW SALMON STREET
SUITE 1600
PORTLAND, OR 97204

EXAMINER	
SHEN, WU CHENG WINSTON	
ART UNIT	**PAPER NUMBER**
1632	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/22/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/516,779	ROZWADOWSKI ET AL.	
	Examiner	Art Unit	
	Wu-Cheng Winston Shen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 December 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *2 and 5-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,22 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner prosecuting this case has changed. All inquiries directed to the application should be directed to examiner W. - C. Winston Shen.

This application 10/516,779 is a 371 of PCT/CA03/00850 06/05/2003.

Election/Restrictions

1. Applicant's response to the Restriction requirement was received on 4/05/2006. Claims 1-23 are pending in the instant application. Applicant's election with traverse of Group II, claims 1, 3, 4, 22, 23, drawn to a method of modifying a target nucleic acid of interest at a target locus within a genome of a host, wherein the host is capable of expressing the RT at the same time as, or after, transforming the host, and a gene targeting construct, is acknowledged.

Claims 2 and 5-21 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 4/28/2006, and the traversal was found not persuasive as recited on page 2-3 of the Non-Final rejection mailed on 06/02/2006.

Status of claims: Claims 1, 3, 4, 22 and 23 are currently under examination.

Information Disclosure Statement

2. As requested by applicants, the second reference of page 13 of the IDS submitted by applicants on 09/19/2005 and considered by previous Examiner, has been considered and signed by the current Examiner.

Claim Rejection - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. The previous rejection of claims 1, 3, 4, 22, and 23 under first paragraph of 35 U.S.C. 112, has been ***withdrawn***. Applicant's arguments filed Dec. 4, 2006 have been fully considered and they are persuasive.

More specifically, Applicants amended claim 1 reciting "A method of modifying a target nucleic acid of interest at a target locus within a genome, comprising: **a)** introducing into a host cell a gene targeting construct (GTC) by transformation of the host cell *in vitro* with a DNA comprising a nucleic acid sequence encoding the GTC, and culturing the host cell or transformed progeny of the host cell so as to: i) express a gene targeting message RNA from the GTC, wherein the message RNA is capable of self-priming reverse transcription by a reverse transcriptase (RT) expressed by the host cell or the transformed progeny of the host cell; ii) wherein at least a portion of the gene targeting message RNA is reverse transcribed to produce a gene targeting substrate (GTS) having a gene targeting nucleotide sequence (GTNS), wherein the GTNS is homologous to the target locus and comprises a sequence modification compared to the target nucleic acid; iii) wherein the GTNS mediates insertion, deletion or substitution of one or more bases of the sequence of the target nucleic acid to produce a sequence modification at the target locus within the genome; and, **b)** selecting a host cell or transformed progeny of the host

cell having the sequence modification at the target locus". The amendments are based on the scope of enablement recited in the Non-Final rejection mailed on 06/02/2006.

Claim Rejection - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

4. Previous rejection of claims 1, 3, 4, 22, and 23 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, has been ***withdrawn*** because applicants have amended claims 1, 3, 4, 22, and 23.

Applicants amended claim 1 reciting "A method of modifying a target nucleic acid of interest at a target locus within a genome, comprising: **a)** introducing into a host cell a gene targeting construct (GTC) by transformation of the host cell *in vitro* with a DNA comprising a nucleic acid sequence encoding the GTC, and culturing the host cell or transformed progeny of the host cell so as to: i) express a gene targeting message RNA from the GTC, wherein the message RNA is capable of self-priming reverse transcription by a reverse transcriptase (RT) expressed by the host cell or the transformed progeny of the host cell; ii) wherein at least a portion of the gene targeting message RNA is reverse transcribed to produce a gene targeting substrate (GTS) having a gene targeting nucleotide sequence (GTNS), wherein the GTNS is homologous to the target locus and comprises a sequence modification compared to the target nucleic acid; iii) wherein the GTNS mediates insertion, deletion or substitution of one or more

bases of the sequence of the target nucleic acid to produce a sequence modification at the target locus within the genome; and, **b)** selecting a host cell or transformed progeny of the host cell having the sequence modification at the target locus". The amendments are based on the scope of enablement recited in the Non-Final rejection mailed on 06/02/2006.

Applicants amended claim 3 reciting "The method of claim 1, wherein further comprising transforming the host cell or the transformed progeny of the host cell is so as to be capable of expressing the RT."

Applicants amended claim 4 reciting "The method of claim 1, wherein the GTC is introduced into the transformed progeny of the host cell by cell fusion."

Applicants amended claim 22 reciting " The method of claim 1, wherein the gene targeting nucleotide sequence comprises one, or more than one, region of 15 to about 500 nucleotides, exhibiting about 70% to about 99% sequence similarity with the target locus sequence, as determined using the following conditions: Program: blastp; Database: nr; Expect 10; filter: default; Alignment: pairwise; Query genetic Codes: Standard (1)."

Applicants amended claim 23 reciting "The method of claim 22, wherein the one or more than one region is of less than 300 nucleotides in length."

Claim Rejection - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. The previous rejection of claims 1, 3, 4, 22, and 23 rejected under 35 U.S.C. 102(e) as being unpatentable by Conrad et al. (Conrad et al. U.S. Patent Application Publication No: 2003/0082800 A1, Publication date, May 1, 2003), priority to 10/091998, hereafter referred to as Conrad et al.), is ***maintained*** of the record for the reasons documented on page 10 of the Non-Final Office action mailed on 06/2/2006. For completeness of this office action, the Non-Final rejection under 35 U.S.C. 102 (e) is reiterated below.

Claims 1,3,4,22, and 23 are rejected under 35 U.S.C. 102(e) as being anticipated by US 2003/0082800 A1 (5.01.2003) priority to (10.09.1998), hereafter referred to as Conrad et al.

Conrad et al. provides guidance on an expression vector for altering expression of a target nucleic acid sequence in a host cell by production of single-stranded cDNA (ssDNA) in the host cell *in vivo*. The expression vector is comprised of a cassette comprising a sequence of interest, an inverted tandem repeat, and a primer binding site 3' to the inverted tandem repeat, and a reverse transcriptase coding gene, and may be transfected into the host cell in a method of sequence modification, such as site directed mutagenesis or gene therapy for therapeutic applications (Abstract; pgph 18). Transcription of the cassette by the host cell produces an RNA template that is reverse transcribed with the product of the RT coding gene to produce ssDNA of a specified sequence. The resulting ssDNA binds to an endogenous target nucleic acid sequence (Abstract). Wherein, hosts that have a sequence modification at the target locus can be selected for (pgph 93). The cassette may be introduced into the host by transformation (pgph 22,45).

Wherein the ssDNA may contain any practical size sequence of interest as an insert, such as 31 bp, 1.2 kb, 2.4 kb in length (Fig. 4A, 4b, pgph 99, 108-117). It is inherent that an insert used for site directed mutagenesis will have at least one bp that is different from the target nucleic acid sequence. Therefore in sequences less than 100 bp long this will provide for 99% or lower sequence similarity. Thus, by teaching all the limitations of the claims as written, Conrad et al. anticipates the instant invention as claimed.

Applicant's arguments filed Dec. 04, 2006 have been fully considered and they are ***not*** persuasive. Specifically, applicants submitted that the cited art (US 2003/0082800 A1) does not teach or suggest the use of self-priming gene targeting message RNA. Instead, in the cited reference, the description of the reverse transcriptase primer, the "primer binding site (PBS)", makes it clear that this primer is NOT self-priming, and in fact requires a tRNA, as set out in paragraph 62 therein, as follows:

> [0062] The primer binding site (PBS) for initiation of priming for cDNA synthesis is located between the 3' IR and the polyadenylation signal. The PBS is a sequence that is complementary to a transfer RNA (tRNA) which is resident within the eukaryotic target cell. In the case of the mouse Maloney reverse transcriptase (MoMULV RT) described herein as being utilized in conjunction with the present invention, the PBS takes advantage of the proline tRNA. The PBS utilized in connection with the presently preferred embodiment of the invention that is described herein was taken from the actual 18 nucleotide sequence region of mouse Moloney virus. Shinnick, T. M., et al., Nucleotide sequence of Moloney murine leukemia virus, 293 Nature 543-548 (1981). [Note that this RT has a similar priming mechanism: HIV-1 reverse transcriptase specifically interacts with the anticodon domain of its cognate primer tRNA. EMBO J 1989 Nov;8(11):3279-3285.] In the case of the RT gene from human immunodeficiency virus that was also tested as noted below, the PBS used was taken from the nucleotide sequence of HIV. Y. Li, et al., 66 J. Virology 6587-6600 (1992). In short, any PBS that is matched to a particular RT is utilized for this purpose. The PBS is exclusively recognized by a primer tRNA that is endogenous to the target cells. Each tRNA has the ability to recognize a unique sequence (i.e., codon) on the mRNA transcript coding for an amino acid, and has the ability to covalently link to a specific amino acid (i.e., the tRNA becomes "charged" when bound to a specific amino acid). However, a primer tRNA, when bound to the mRNA transcript PBS and not covalently linked with an amino acid

> (i.e., "uncharged"), may be used to initiate ssDNA synthesis by the RT. For example, the MoMULV RT used in the examples described herein recognizes and uses an uncharged lysine tRNA that in turn recognizes and binds to its unique sequence in the PBS. Thus, each PBS incorporated into the expression system of the present invention must contain the unique sequence recognized by the primer tRNA, and the primer tRNA must be a primer tRNA that is recognized by the particular RT utilized.

The cited prior art does not therefore teach or suggest the use of a gene-targeting message RNA that is capable of self-priming reverse transcription. Accordingly, it is submitted that the cited art does not anticipate the presently claimed invention. In this context, it is relevant that there is an important potential difficulty associated with the approach to RT priming taken in the cited art. While self-priming in accordance with the present invention may be made to be effective to mediate reverse transcription in the nucleus, particularly where the RT comprises a nuclear localization signal sequence, a primer that depends on the presence of a particular tRNA may be ineffective in the nucleus when the tRNA is not present in the nucleus in adequate amounts.

Response to Applicants' Arguments

Regarding the claimed novelty of the instant invention by the limitation "gene targeting message RNA that is capable of self-priming reverse transcription" recited in claim 1 of instant application, it is noted that whether the recited mRNA will require a tRNA molecule for a reverse transcriptase to initiate cDNA synthesis is dependent on the *inherent properties* of the 5' sequences of the mRNA. At the time of the filing of instant application, cDNA synthesis by reverse transcriptase via either a tRNA molecule binding to the 3' end of the mRNA or the 5' end of the mRNA bind to its own 3' end via a looping mechanism was known and evidenced in the art. For instance, Levin teach the inherent properties of render the Tf1 mRNA undergoing a

self-priming mechanism of reverse transcription (See abstract, Fig. 1, page 3312, Levin, A novel mechanism of self-primed reverse transcription defines a new family of retroelements. *Mol Cell Biol.* 15(6): 3310-7, 1995).

It is further noted that the mechanistic features regarding how a cDNA corresponding to a given mRNA molecule being synthesized by a reverse transcriptase does not alter the claimed method of modifying a target nucleic acid of interest at a target locus with a genome recited in claim 1 of instant application.

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Conclusion

7. No claim is allowed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

PETER PARAS, JR.
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Wu-Cheng Winston Shen, Ph. D.
Patent Examiner
Art Unit 1632